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Deletion 4q21/4q22 Syndrome: Two Patients With De Novo 4q21.3q23 and 4q13.2q23 Deletions

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We report on 2 patients with de novo proximal interstitial deletions of the long arm of chromosome 4: in one the deletion resulted in monosomy (4)(q21.3q23), in the other it produced monosomy (4)(q13.2q23). Review of 9 cases of deletions involving the 4q21/4q22 region reported previously detected a characteristic phenotype in 8 patients. This phenotype was present in our patients. We conclude that the deletion in the 4q21/4q22 region results in a specific clinical syndrome associated with central nervous system overgrowth that may be a result of anomalous imprinting in the 4q21/4q22 region. Am. J. Med. Genet. 69:400–405, 1997.

KEY WORDS: human chromosome 4; chromosome deletion; hydrocephalus; megalencephaly; alphafetoprotein

INTRODUCTION

Interstitial deletions of the long arm of chromosome 4 have been reported in 32 cases with variable clinical manifestations [Lacassie et al, 1977; Mikkelsen et al., 1977; McDermott et al, 1980; Ligutic et al, 1981; Mitchell et al, 1981; Campbell et al, 1986; Del Valle Torrado et al, 1982; Fagan and Gill, 1989; Lech et al., 1984; Hoo et al., 1986; Butler et al., 1987; Motegi et al., 1988; Beall et al., 1988; Chudley et al., 1988; Yamamoto, et al., 1989; Curtis et al., 1989; Curtis et al., 1990; Koppitch et al., 1990; Raczenbek et al., 1991; Rose et al., 1991; Wakui et al., 1991; Engelen et al., 1992; Sarda et al., 1992; Vaux et al., 1992; Sijmons et al., 1993; Copelli et al., 1995; Kulharya et al., 1995]. Distal interstitial and terminal 4q deletions result in a characteristic, well-described phenotype associated with the loss of bands (4)(q31q33) [Lin et al., 1988]. The phenotype associated with more proximal deletions is more variable. Kulharya et al. [1995], in reporting 2 patients with interstitial 4q deletions, proposed the existence of distinct proximal and distal interstitial 4q deletion syndromes. We report on two patients with proximal interstitial deletions of 4q and a characteristic phenotype. Eight patients with similar clinical findings have been reported previously and in seven of these the common cytogenetic abnormality reported was the loss of the distal part of band 4q21 and band 4q22, deleted in all patients as part of larger deletions.

CLINICAL REPORTS AND RESULTS

Patient 1

The first patient was referred at age 6 1/2 months for hypotonia, macrocephaly, and developmental delay. He was born to a 28-year-old G2P1 woman by spontaneous vaginal vertex delivery at 39 weeks of gestation. Birth weight was 3,870 g (75th centile), length was 52 cm (50th centile), and occipitofrontal head circumference (OFC) was 40 cm (>97th centile). The pregnancy was complicated by first trimester bleeding. Elevated maternal alphafetoprotein (+2.68 MoM at 17 weeks and 5 days) was investigated by ultrasound, which showed cerebral ventricles at the upper limit of normal and no evidence of a neural tube defect. The neonatal course was uncomplicated. The family history was noncontributory, and parents were non-consanguineous.

On physical examination at the age of 6 1/2 months, the patient was an unusual looking child with large head with prominent occiput and frontal bossing (Figs. 1 and 2). OFC was 50.5 cm (>97th centile), weight 7.2 kg (10th centile), and length 64 cm (3rd centile). The anterior fontanelle was irregular in shape, measuring 6 cm by 10 cm, and extending onto the forehead; there was bilateral temporal narrowing of the head. Facial anomalies included hypertelorism, small eyes, broad nasal bridge, small nose, and small, simple ears; he had small hands and feet with tapering fingers (Fig. 3). Cardiovascular system, chest and abdomen were normal. The testes were descended, and the penis was small. He was profoundly hypotonic; deep tendon reflexes were present and 3+ throughout, muscle

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Fig. 1. Patient 1: head, anterior.

Fig. 2. Patient 1: head, profile.

strength was decreased. Cranial nerve function was normal for age. Fundoscopic findings were normal and no cataracts or abnormalities of the anterior chamber were present. Development was delayed: at 6 months he fixed and followed inconsistently, had no social smile, was not babbling, and had no head control.

Somatosensory evoked potentials and auditory brainstem evoked responses were normal; visual evoked potentials were mildly abnormal. Skeletal radiographs showed a large skull with slightly separated sutures, and a J-shaped sella. There were 11 pairs of ribs and a hemivertebra at T4, with scoliosis convex to the left. The long bones were normal. Abdominal ultrasound showed a 7 mm cyst in the cortex of the right kidney. Head CT and brain MRI showed a structurally normal brain with megalencephaly and mild increase in the subarachnoid spaces suggestive of mild extraventricular communicating hydrocephalus (Fig. 4).

Results of biochemical investigations, including serum very long chain fatty acids, phytanic acids, serum triglycerides, cholesterol, quantitative amino acids, and urinary oligosaccharides, mucopolysaccharides, and organic acids were normal.

Feeding difficulties present from birth persisted. A feeding study showed oropharyngeal incoordination and gastroesophageal reflux to the level of the clavicles. At the age of 8 months, a percutaneous gastrostomy tube was placed to facilitate feeding. Growth parameters at that time remained at the same centiles: OFC 51.5 cm (>97th centile), length 67 cm (10th centile), and weight 7.7 kg (3rd centile).

Patient 2

He was born to a 30-year-old G2P1 woman by cesarean section for cephalopelvic disproportion at 37 weeks gestation following an uncomplicated pregnancy. The parents were non-consanguineous and of Italian descent. Birth weight was 2,600 g (<50th centile), length 44 cm (<3rd centile), and OFC 35 cm (90th centile).

At birth he was noted to have frontal bossing, large anterior fontanelle, occipital encephalocele, high arched palate with small posterior cleft, small nose with flat nasal bridge, small ears, small chin, bilateral inguinal hernias, small penis, absent scrotal rugae, small broad hands with bilateral single palmar creases and clinodactyly, rocker bottom feet, and a suggestion of proximal limb shortening. There was no organomegaly. Spinal radiographs showed a hemivertebra at T6, and 11 pairs of ribs. Echocardiogram demonstrated a ventricular septal defect with sigmoid septum, and a large patent ductus arteriosus. Renal ultrasound showed no abnormalities of the kidneys or the genitourinary system. CT of the head showed a high occipital encephalocele with hypoplasia of the right cerebellar hemisphere, high insertion of the tentorium with a cerebrospinal fluid communication with the encephalo-

Fig. 3. Patient 1: full body.

cele cavity, and bilateral subependymal cysts (Fig. 5). The encephalocele was resected at seven days.

By 3 months of age the megalencephaly became absolute: his OFC was 40.5 cm (>95th centile), while his weight was 4.4 kg (10th centile), and length was 48.5 cm (<3rd centile). Ultrasonographic examination of the head showed no ventricular dilatation or evidence of hydrocephalus. A barium swallow showed gastroesophageal reflux to the level of the of clavicles. The patient developed apneic spells, and died of respiratory arrest at the age of seven months. No autopsy was performed.

MATERIALS AND METHODS

Cytogenetic Analyses

High resolution chromosome preparations were obtained from lymphocytes cultured using ethidium bromide [Ikeuchi, 1984] and routine GTG banding methods were performed. Cytogenetic analysis demonstrated an interstitial deletion of 4q in both patients (Fig. 6). In patient 1, the deletion was interpreted to include bands 4q21.3 → 4q23, resulting in a 46, XY, del(4)(q21.3q23) karyotype. In patient 2, the deletion was interpreted to include bands 4q13.2 → 4q23 with a resulting 46, XY, del(4)(q13.2q23) karyotype. Karyotypes were normal in parents of both patients.

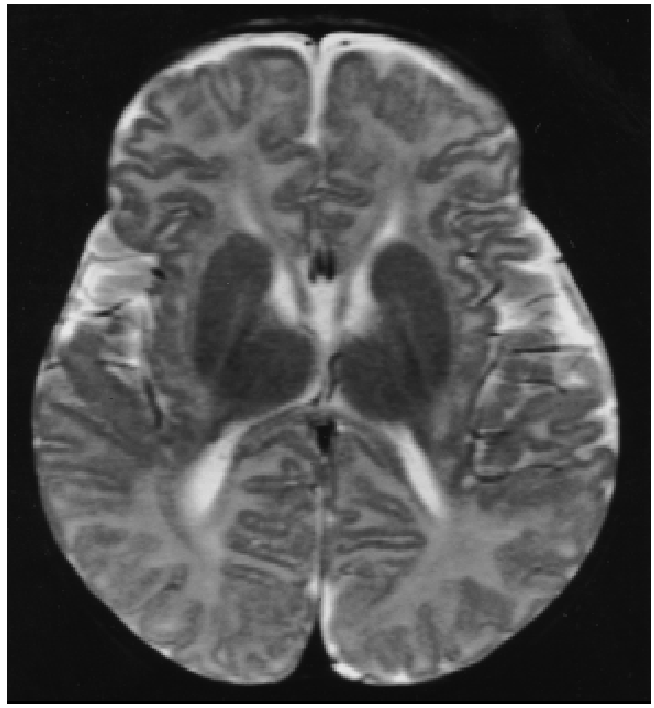

Fig. 4. Patient 1: head MRI showing megalencephaly.

DISCUSSION

Eight of nine patients with deletions of the 4q21/4q22 region have been reported (4)(q13q22) [McDermott et al., 1980], (4)(q21.1q25) [Mitchell et al., (patient 7) 1981], (4)(q22q25) [Butler et al., 1987], (4)(q21.1q22.1) [Fagan and Gill, 1989], (4)(q21q25) [Rose et al., 1991], (4)(q21.1q25) [Kulharya et al. (patient 1), 1995], including two prenatal diagnoses with therapeutic terminations: (4)(q21q27) [Campbell et al., 1986] and (4)(q22q26) [Koppitch et al., 1990], had a recognizable phenotype similar to the one seen in our patients. The one remaining patient with deletion (4)(q21.3q26), patient 6 reported by Mitchell et al. [1981], did not have macrocephaly and had different facial anomalies. One patient with a reported (4)(q12q21.1) deletion, with a breakpoint in the proximal part of 4q21 [Beall et al., 1988] shared with our patients the findings of relative megalencephaly, frontal bossing, prominent occiput, low-set ears, micrognathia; short sternum, and small hands and feet. The common clinical findings in 10 patients: 2 from this report, 7 with larger deletions including distal band 4q21 and band 4q22, and one with deletion (4)(q12q21.1) who clinically resembles the patients with 4q21/4q22 deletion, are presented in Table 1.

Campbell et al. [1986] reported a fetus diagnosed prenatally with deletion (4)(q21q27), and proposed the "interstitial 4q-" phenotype consisting of mid-face asymmetry and hypoplasia, cleft lip and palate, micro-

Fig. 5. Patient 2: head CT showing encephalocele and high insertion of the tentorium.

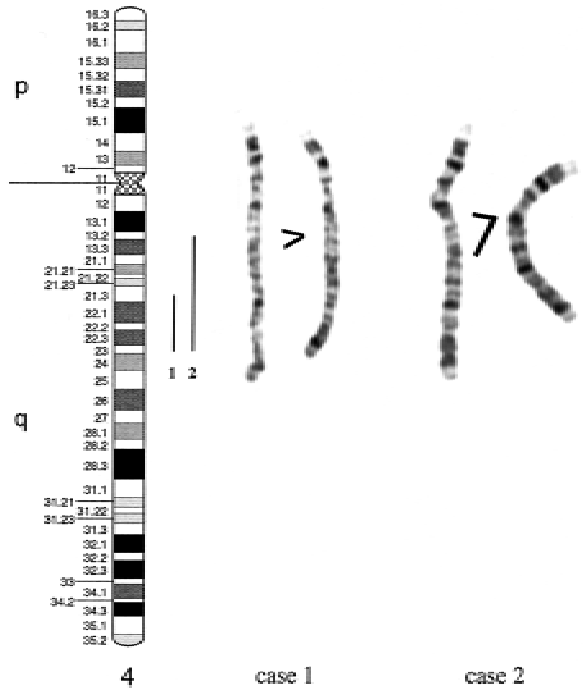

Fig. 6. Partial karyotypes of patients 1 and 2.

gnathia, abnormal auricles, abnormalities of finger and toes, and cardiac anomalies. However, this review did not differentiate between proximal and more distal interstitial deletions. Of note, this prenatal diagnosis followed the detection of high maternal serum alphafetoprotein level at 17 weeks gestation. The mechanism of the elevated alphafetoprotein is not known.

This clinical syndrome consists of absolute or relative macrocephaly secondary to megalencephaly with a characteristic head shape and facial appearance, small hands and feet, short limbs, profound hypotonia, feeding difficulties, failure to thrive, mental retardation, and severe developmental delay. Both sexes (M:F 7:5) are affected. Life expectancy is reduced with death in the first year of life. The cause of death was respiratory arrest in two patients [Mitchell et al., 1981 (patient 7); Butler et al., 1987], cardiorespiratory arrest in a setting of progressive hydrocephalus [Kulharya et al., 1995], and complex congenital heart anomalies [Fagan and Gill, 1989]. This syndrome does not include piebaldism (4q12) [Giebel and Spritz, 1991] or Rieger anomaly (4q25) [Murray et al., 1992], and is distinct from the distal-terminal (4q33 → qter) deletions delineated by Lin et al. [1988], and the distal interstitial 4q deletions as defined by Kulharya et al. [1995]. The following were noted in patients with deletions spanning the distal 4q21/4q22 region reported in the literature: hypoplastic nipples (4 patients), seizures (3), mild ventricular dilatation (3), small renal cysts (single or multiple) (2), small nails (2), overlapping toes (3). Abnormalities reported in one patient only included esotropia, exotropia, cleft alveolar ridge, complete bilateral cleft lip and palate, severe hearing loss, agenesis of corpus callosum, hydrocephalus, accessory hypoplastic

TABLE I. Manifestations of 4q21/4q22 Deletion in Ten Patients*

Manifestation	Patient 1	Patient 2	Beall [1988]	Number of patients affected/ reported
Death <1 year	?	+	–	5/9[a]
Developmental delay	+	+	+	9/9[a]
Hypotonia	+	+	+	9/9[a]
Minor anomalies				
Macrocephaly	+	+	+	9/10[b]
Frontal bossing	+	+	+	10/10
Small nose	+	+	+	7/10
Flat nasal bridge	+	+	+	9/10
Large ant. fontanelle	+	+	+	7/10
Malformed ears	+	+	+	10/10
Micrognathia	+	+	+	9/10
Skeletal				
Axial anomaly	+	+	–	5/10[c]
Small digits	+	+	+	9/10
Short limbs	+	+	+	9/10
Central nervous system				
Hydrocephalus	+	–	–	4/10

*McDermott et al., 1980; Mitchell et al., (patient 7) 1981; Campbell et al., 1986; Butler et al., 1987; Beall et al., 1988; Koppitch et al., 1990; Rose et al., 1991; Kulharya et al., (patient 1) 1995.
[a]Does not include two prenatal terminations.
[b]No head circumference information [Campbell et al., 1986].
[c]Eleven pairs of ribs, butterfly vertebrae, hemivertebrae, short sternum.

digits on fifth fingers, atrioventricular septal defect with small pulmonary vessels, atrial septal defect, preductal coarctation of the aorta with double superior vena cava, congenital hypothyroidism, complete laryngeal cleft, malrotation of the gut, umbilical hernia, and large labia minora.

A characteristic finding in the seven of nine patients in whom head circumference was reported was megalencephaly. Macrocephaly has been reported in association with a number of chromosomal abnormalities: partial duplication (1)(q25q32) [Schinzel, 1984], partial duplication (5)(p13.32p14.2) [Rethoré et al., 1989], and partial duplication (12)(q21.2qter) [Pratt and Bulugahapitiya, 1983], partial deletion (9)(q32qter) [Kargas et al., 1987], and terminal deletion of (5)(q35.3) [Stratton et al., 1994]. In distal 4q21/4q22 deletion syndrome the head was large as result of increased brain size which was otherwise structurally normal. Migrational abnormalities were not detected on brain imaging studies in our two patients, but subtle neuronal migration abnormalities may be missed at such an early age. There was minimal increase of extraventricular fluid volume in patient 1, and encephalocele with no evidence of hydrocephalus in patient 2. This appears to be an overgrowth syndrome limited to the brain. Overgrowth syndromes have been associated with anomalies of imprinting [Weksberg, et al. 1993] and it is possible that the loss of normal imprinting of a gene in the proximal 4q region (distal region of band 4q21 or band 4q22), responsible for brain growth, results in abnormally accelerated fetal brain growth. Chromosome 4 is considered to be syntenic with mouse chromosomes 3 and 5 [Riess et al., 1994] and imprinting for mouse chromosome 5 has been suggested [Cattanach and Beechey, 1990]. Lack of detailed deletion breakpoints in reported patients makes it difficult to define the region responsible for the described phenotypic features. Further molecular studies of this region are required in order to determine the exact deletion breakpoints and the contribution, if any, of the parental origin of the deleted chromosome.

In summary, we report two cases of interstitial deletion of the proximal long arm of chromosome 4 involving the 4q21/4q22 region by cytogenetic analyses. We conclude that interstitial deletions involving the 4q21/4q22 region are associated with a distinct set of cerebral, facial, and skeletal anomalies and with developmental retardation, and that this proximal deletion syndrome is distinct from the more distal and terminal 4q deletion syndromes. Loss of imprinting of this region may be responsible for the brain overgrowth observed in these patients.

ADDENDUM

Patient 1 died at home at the age of 21 months from presumed pneumonia. In accordance with patients' wishes, postmortens examination was not performed; however a skin fibroblast culture was established.

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